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EXAMINER
SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

SW

Office Action Summary	Application No.	Applicant(s)	
	09/627,787	UHLMANN ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *01 April 0226*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *3 and 7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-6 and 8-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 2/26/04.

Claims 1-26 are pending.

Claims 3, 6, and 7 were withdrawn from consideration in Paper No. 15 as being drawn to nonelected species. Applicant timely traversed in Paper No. 14.

Claim 6 was rejoined in the previous Office Action because it was anticipated by the Lucas reference that had been applied to claims 1, 11, 12, and 16-26.

Claims 1, 2, 4-6, and 8-26, and the species of the invention wherein the molecule to be transported is an oligonucleotide or a compound of less than 500 D are under consideration in this Office Action.

Rejections Withdrawn

The rejection of claims 8, 11-14, and 16-26 over Lucas in view of either Choi et al (US patent 5,820,873, issued 10/13/98) or Norden et al (US Patent 6,228,982, issued 5/8/01) is withdrawn after further consideration. These references do not provide adequate motivation to use a carbonyl or thioamide linker in conjunction with an aryl group of formula I.

The rejection of claims 8, 10, 11, 12, 15-26 over Lucas et al (5,698,411, issued 12/16/1997) in view of Pitt et al (Journal of General Microbiology (1969), 56(3), 321-9) and either Choi et al (US patent 5,820,873, issued 10/13/98) or Norden et al (US Patent 6,228,982, issued 5/8/01) is withdrawn for the same reason.

Claim Objections

Claim 9 is objected to because it does not end in a period.

Claim 17 is objected to because the phrase in item a) "preparing a the conjugate" is ungrammatical. Deletion of 'a' is suggested

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 1-8 and 10-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-8 and 10-26 have been amended to require that "the attachment between the aryl radical and the molecule to be transported is stable in vivo." The issue in this rejection is the scope of the phrase "stable in vivo." This phrase is reasonably interpreted as embracing stability for any length of time in any in vivo location. At page 13 of the response, Applicant states that this "amendment is supported throughout the application as a whole, for example, at page 6, lines 1-19, page 23, lines 11-16, and in original claim 17." None of these passages provides written support for the entire scope

of this phrase. Instead the specification at page 6 teaches that "the covalent bond between the aryl radical and the oligonucleotide is preserved during uptake into the cell", and at page 23 and original claim 17 "the conjugate is transported into the cell without the aryl radical being cleaved off." As such, the specification supports only "during uptake into the cell" and " transported into the cell" as the in vivo location for stability and the length of time for which the compound is stable. In contrast, the claims as amended read on stability of the attachment between the aryl radical and the molecule to be transported in any compartment in vivo, including extracellular compartments such as the blood or the gastrointestinal tract, and for any length of time, not just during transport. As such, one of skill in the art could not conclude that Applicant was in possession of the claimed invention at the time the application was filed.

Written Description

Claims 1, 2, 4-6, and 10-26 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 2, 4-6, and 10-26 are drawn to the genus of conjugates comprising an aryl radical of formula I as set forth in claim 1, wherein the attachment between the aryl radical and a molecule to be transported is stable in vivo. The "aryl" portion of the

radical may be any group containing at least on ring having aromatic character. The remaining constituents of the radical ("X", "Y", and "R1") are given limiting definitions in the claims. So the breadth of the claimed genus is equal to the breadth of the group containing at least one ring having aromatic character, with the added functional limitation wherein the attachment between the aryl radical and a molecule to be transported is stable in vivo. Neither the claims nor the specification explicitly disclose any correlation between any structure and the added functional requirement.

The specification at page 4, line 25 to page 5, line 34 indicates that the essence of the invention is that "aryl ester conjugates of a certain structure" have "advantageous properties" such as improved duration and efficiency of cellular uptake, and improved intracellular distribution. At page 6, lines 1-14 the specification discloses that aryl ester-oligonucleotide conjugates according to formula I were known in the prior art (Iyer et al (Bioorg. Med. Chem. 7(7): 871/876, 1997)), but "in contrast to the conjugates according to the instant invention, no accelerated uptake of the oligonucleotides into the cells and likewise no changed intracellular distribution of the oligonucleotides have been found for these prodrugs."

Given the teachings of the specification, it is clear that Applicant considers the invention to be the discovery of an aryl radical conjugate that affords improved cellular uptake and intracellular distribution characteristics. However, while the specification teaches that "all aryl conjugates of a certain structure" will provide the advantages of the invention, the specification fails to adequately describe that "certain structure". For example, the specification fails to teach why the structures of Iyer (1997), while falling

within the structural limitations set forth in claim 1, fail to have the improved functional characteristics that Applicant associates with the invention, e.g. improved cellular uptake and intracellular distribution characteristics, and stability in vivo.

The specification reduces to practice 11 species of the invention in Figs. 2a and 2b. These structures differ from the structure of Iyer in that the molecule to be delivered is linked to the aryl group via a carbonyl or a thioamide group. This is the only structural element that these compounds have in common that is absent from the compounds of Iyer.

Applicant is referred to the Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at www.uspto.gov). The following passage is particularly relevant.

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

The 11 species reduced to practice in the specification correspond to the subgenus recited in claim 8 and dependents, i.e. those conjugates in which the molecule to be transported is attached to the aryl group via a carbonyl or thioamide linkage. These species are deemed to provide an adequate written description of that

subgenus. However, the only disclosed examples of the genus of conjugates that lack the carbonyl or thioamide (i.e. the conjugates of Iyer (1997)), do not appear to have the functional characteristics that Applicant associates with the invention. The specification fails to reduce any of these structures to practice and fails to teach what "certain structure" of these aryl conjugates is required for the functional characteristics that Applicant perceives as the contribution over the prior art. In the absence of any reduction to practice or teaching of a correlation between any required structural characteristic of these aryl radicals and the functional characteristics of the conjugates, this portion of the genus is not adequately described, and one of skill in the art could not conclude that Applicant was in possession of the claimed genus of aryl radicals invention at the time of filing. This rejection can be overcome by requiring in all claims the carbonyl or thioamide linkages as set forth in claim 8.

Response to Arguments

Applicant's arguments filed 2/26/04 have been fully considered but they are not persuasive.

Applicant argues that the rejection is moot because the claims now require that "the attachment between the aryl radical and the molecule to be transported is stable in vivo". In essence, Applicant argues that the claimed genus has been narrowed to exclude the structures of Iyer which, while meeting the structural requirements of the claims, allegedly do not meet the functional requirements, i.e. stable in vivo. This is unpersuasive for several reasons. First, the specification fails to teach what structural

features are required to furnish the functional feature of "stable in vivo", and as noted in the rejection, the specification also fails to teach what structural features are required to provide improved cellular uptake and intracellular distribution characteristics. Applicant appears to argue in the paragraph bridging pages 15 and 16 of the response that these structural features are well known to those of ordinary skill in the art. However, this opinion is unsupported by evidence and so is unpersuasive. Applicant argues that they need not identify such structural features (i.e. linkers) and notes that the Office action states that the use of linkers is routine in the art and is a matter of design choice. This is unpersuasive because the claims now require a specific function of the linker, i.e. it must be stable in vivo. Further note that the Office's position referred to by Applicant was taken in the obviousness rejection of claim 8, which has been withdrawn.

Applicant's argument at page 16 that written description rejections based on original claims should be rare, because there is a strong presumption that the application supports them, is unpersuasive because Applicant has not been able to point to any place in the specification that adequately supports the claimed genus. The written description analysis has been carried out as stipulated in the Guidelines on Written Description, as discussed above. The Office has shifted the burden to Applicant to either identify support for the claimed genus or amend the claims such that they are adequately supported. Merely stating that written description rejections of original claims should be rare is insufficient to overcome the rejection.

Finally, Applicant appears to argue that the "aryl ester conjugates of a certain structure" that have "advantageous properties" such as improved duration and

efficiency of cellular uptake, and improved intracellular distribution are adequately described in the summary of the invention and "elsewhere in the application and figures". This is unpersuasive because Applicant has failed to point to exactly where this description is located. The rejection is based upon a thorough reading of the specification. If Applicant asserts that the specification contains material that adequately supports the claims, then such an assertion should be supported by a recitation by page and line number where this information can be found. In the absence of such support, the Office's position continues to be that the specification fails to adequately support the genus of attachments between the aryl radical and the molecule to be transported that are stable in vivo, and the genus of aryl radical conjugates that afford improved cellular uptake and intracellular distribution characteristics but which lack a carbonyl or thioamide linker. For these reasons the rejection is maintained.

Enablement

Claims 1-8 and 10-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for conjugates according to claims 1-8 and 10-26 wherein the attachments between aryl radicals and molecules to be transported is not cleaved during transport into the cell, does not reasonably provide enablement for embodiments of these claims in which the attachment is stable indefinitely in vivo. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 1-8 and 10-26 are drawn to conjugates comprising an aryl group and a molecule to be transported. The claims have been amended to require that "the attachment between the aryl radical and the molecule to be transported is stable in vivo." The issue in this rejection is the scope of the phrase "stable in vivo." This phrase is reasonably interpreted as embracing stability for any length of time in any in vivo location. The specification at page 6, lines 1-19, page 23, lines 11-16, and in original claim 17 assert that the claimed attachments are stable "during uptake into the cell" and during transport into the cell. However, the specification provides no evidence that the claimed attachments are stable indefinitely in vivo.

The prior art taught that structures that fall within the claimed genus are not stable indefinitely in vivo under certain conditions. See Iyer et al (1997) who teach that such attachments are bioreversible allowing release of the molecule to be delivered (see above), or Lucas et al (US Patent 5,698,411, issued 12/16/1997) who designed compositions that have the claimed attachment structures but which are biodegradable in the presence of certain cellular enzymes (see below under 35 USC 102 and 103 rejections).

The specification fails to teach any working example of an attachment that confers stability indefinitely in all locations in vivo. While Applicant is not required to disclose that which is well known in the art, there is an obligation to disclose critical elements of the invention as well as how to use these elements. In Genentech, Inc, v

Novo Nordisk A/S, the court found that when the specification omits any specific starting material required to practice an invention, or the conditions under which a process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, the identification of attachments that are indefinitely stable in vivo cannot be overlooked in the process of providing an enabling disclosure, particularly in view of the prior art which shows that compounds that fall within the structural limitations set forth in the claims are not stable indefinitely in some cells. As such, one of skill in the art would have to perform undue experimentation in order to practice the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 6, 11, 12, 16-26 stand rejected under 35 U.S.C. 102(b) as being anticipated by Lucas et al (US Patent 5,698,411, issued 12/16/1997).

Lucas teaches compositions for assaying enzyme activity in intact cells. The compositions comprise a conjugate between an aryl moiety and one or more leaving groups. See abstract. The leaving groups may be e.g. lipids or fatty acids of less than 500 Daltons. See abstract; column 9, line 16 to column 10, line 2; and column 23, lines 43-65. See also attached search result showing an aryl group with two amide groups attached which anticipates claims 1 and 6 when X=N. Note also that the analogous compound comprising fatty acid esters would anticipate claim 1 when, X=O. In this rejection, one fatty acid or amide moiety accounts for R1 and the other is considered to be the molecule to be delivered. The compositions are transported into both human and tumor cells. See paragraphs 113 and 107. The compositions may be admixed to provide proper osmolality and may contain additives such as enzyme inhibitors. See column 28, lines 15-41. Claims 24-26 are included in this rejection because the compositions of Lucas meet the physical characteristics required by these claims.

Thus Lucas anticipates the claims.

Response to Arguments

Applicant's arguments filed 2/26/04 have been fully considered but they are not persuasive.

Applicant argues that Lucas fails to teach the claim limitation requiring that "the attachment between the aryl radical and the molecule to be transported is stable in vivo", because the compound of Lucas is designed to be hydrolyzed in cells. This is unpersuasive because Applicant has provided no evidence to indicate that the compound of Lucas would be unstable in all in vivo locations, e.g. in the blood.

Furthermore, because the compound of Lucas is designed as a substrate to detect enzyme activity, the stability of the compound is directly dependent on the level of activity of the target enzyme in the assay. If the compound were administered to a cell for the purpose of determining whether a given enzyme was absent or inactive, the compound would be stable if the enzyme was not present or had been metabolically or genetically inactivated. See e.g. Lucas at column 4, line 45 to column 6, line 41.

Applicant argues further that Lucas does not anticipate any of claims 1, 6, 11, 12, or 16-26 because the "broad, generic disclosure" of Lucas provides so many choices in terms of moieties to attach to the aryl group that one of skill in the art could not clearly envision the claimed genus within the reference's broad disclosure. Applicant relies for support on *In re Ruschig*. This argument is unpersuasive because a disclosed species anticipates a genus. See MPEP 2131.02. In this case, Lucas teaches by structure at least one compound that anticipates the claimed structure when X=O, Y=O, R1 = substituted C5 alkyl, and n=1. See attached search result. Note that this argument also appears inconsistent with Applicant's position in the response to the written description rejection in which Applicant indicates that their own broad, generic disclosure adequately describes the claimed genus.

For these reasons the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4-6, 10, and 22-26 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Iyer et al (Bioorg. Med. Chem. 7(7): 871/876, 1997), in view of Iyer et al (Bioorg. Med. Chem. 4(20): 2471-2476, 1994), and Iyer et al (Bioorg. Med. Chem. 6(16): 1917-1922, 1996).

Iyer(1997) teaches phosphorothioate or phosphodiester oligonucleotides comprising acyloxyaryl conjugates at the internucleotide linkages. See Fig. 2, and Scheme 1 on page 872. The oligonucleotides are intended to be delivered to cells. See page 871, lines 1-6 of first paragraph.

Iyer does not teach a conjugate comprising a group corresponding to instantly claimed group R1 which is a C5-C22 alkyl radical. Instead Iyer teaches a t-butyl R1 group. See scheme 1 on page 872. Iyer (1997) is silent as to the pH at which reaction between the molecule to be transported and the aryl radical is carried out.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the composition of Iyer (1997) by substituting C5-C22 alkyl radicals for the isobutyl radical, because they differ from the group of Iyer only by the addition of -CH2- groups, and because the stated function of the groups of Iyer is to provide lipophilicity to the oligonucleotide for improved cellular uptake. See Iyer (1994) paragraph bridging pages 2471 and 2472, and Iyer (1996) page 1917, lines 9-12. One of ordinary skill in the art would expect the instant C5-C22 groups to provide this function, so substitution would preserve the stated function of the t-butyl group of Iyer. MPEP 2144.09 states that a prima facie case of obviousness may be made when

chemical compounds have very close structural similarities and similar utilities. "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." In re Payne, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). See In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) (discussed in more detail below) and In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991). Further, compounds differing regularly by the successive addition of the same chemical group, e.g., by -CH2- groups, are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. In re Wilder, 563 F.2d 457, 195 USPQ 426 (CCPA 1977).

Pertinent to claims 22 and 23, the Iyer references teach admixing phosphorothioate and phosphodiester versions of the conjugates as well as adding an aqueous buffer excipient. See (paragraph bridging pages 873 and 874.

Claims 24 and 25 are included in this rejection because the compositions of Iyer meet the physical characteristics required by these claims. For example, absent evidence to the contrary, the modified oligonucleotides could be considered to be diagnostic compositions as required by claim 25, because they would be useful in hybridization assays to detect their target nucleic acids.

Pertinent to claim 26, Iyer (1997) does not explicitly teach the organization of the compositions into a kit. However, it would have been obvious to one of ordinary skill in the art at the time of the invention to organize the compositions into a kit because one of

skill in the art appreciates that organizing experimental reagents prior to use is standard laboratory practice which reduces the frequency of errors.

Thus the invention as a whole was prima facie obvious.

Claims 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iyer (1997), Iyer (1996), and Iyer (1994) as applied to claims 1, 2, 4, 5, 10, 11, 13-15, and 22-26 above, and further in view of either one of Yamamoto et al (Genetics (1992) 131(4): 811-819), or White et al (Antimicrob. Agents and Chemother. (1997) 41(12): 2699-2704).

The Iyer references can be combined to render obvious oligonucleotides with acyloxyaryl modifications, intended for delivery to cells. The purposes of the modification include improving cellular uptake by increasing the hydrophobic character of the oligonucleotides, and increasing stability by inhibiting nucleolytic degradation. See page 1917, lines 11-16 of Iyer (1996), page 2472, lines 3-8 of Iyer (1994).

These references do not explicitly disclose a method of delivering oligonucleotides across a cell membrane, particularly to bacterial or yeast cells.

Yamamoto teaches a method of delivering antisense oligonucleotides to yeast cells.

White teaches a method of delivering antisense oligonucleotides to E. coli cells.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the antisense oligonucleotides of Yamamoto or White as taught by Iyer (1997) in order to improve subsequent cellular oligonucleotide uptake and stability.

Thus the invention as a whole was prima facie obvious.

Claims 16-21 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Iyer (1997), Iyer (1996), and Iyer (1994) as applied to claims 1, 2, 4, 5, 10, 11, 13-15, and 22-26 above, and further in view of Higgins et al (PNAS (1993) 90: 9901-9905).

The Iyer references can be combined to render obvious oligonucleotides with acyloxyaryl modifications, intended for delivery to cells. The purposes of the modification include improving cellular uptake by increasing the hydrophobic character of the oligonucleotides, and increasing stability by inhibiting nucleolytic degradation. See page 1917, lines 11-16 of Iyer (1997).

These references do not explicitly disclose delivery across a cell membrane, particularly to a human cell (claim 20) or a tumor cell (claim 21).

Higgins teaches a method of delivering antisense oligonucleotides to human tumor cells in vitro and to mouse tumor cell in vivo. The oligonucleotides administered in vivo were prepared in phosphate buffered saline and are considered to be a pharmaceutical composition. See abstract; "Tumorigenicity Assays" on pages 9901 and 9902; Table 1 on page 9902; and Fig. 2 on page 9903.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the oligonucleotides of Higgins as taught the Iyer references in order to improve delivery and stability of the oligonucleotides.

Thus the invention as a whole was prima facie obvious.

Claims 11, 13, and 14 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lucas et al (5,698,411, issued 12/16/1997).

Lucas teaches compositions for assaying enzyme activity in intact cells. The compositions comprise a conjugate between an aryl moiety and one or more leaving groups. See abstract. The leaving groups may be e.g. lipids or fatty acids. See

abstract; column 9, line 16 to column 10, line 2; and column 23, lines 18 to column 24, line 10. See also attached search result showing an aryl group with two amide groups attached which anticipates claim 1 when X=N. Note also that the analogous compound comprising fatty acid esters would anticipate claim 1 when, X=O. In this rejection, one fatty acid or amide moiety accounts for R1 and the other is considered to be the molecule to be delivered.

Lucas is silent as to the pH of the reaction conditions under which the aryl moiety and the leaving group are joined, however the pH of the reaction is considered to be a result effective variable that is routinely optimized. Absent evidence to the contrary, it would have been obvious to perform the reaction at pH 7.0.

Claims 1, 2, 4, 5, 10, 11, 12, 15-26 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lucas et al (5,698,411, issued 12/16/1997) in view of Pitt et al (Journal of General Microbiology (1969), 56(3), 321-9).

Lucas teaches compositions for assaying enzyme activity in intact cells. The compositions comprise a conjugate between an aryl moiety and one or more leaving groups. See abstract. The leaving groups may be e.g. polysaccharides, oligopeptides, lipids, fatty acids, nucleotides, polynucleotides, and combinations thereof. See abstract; column 9, line 16 to column 10, line 2; and column 23, lines 18 to column 24, line 10. See also attached search result showing an aryl group with two amide groups attached which renders obvious claim 1 when X=N. Note also that the analogous compound comprising fatty acid esters would renders obvious claim 1 when, X=O. Instant claims

requiring that the delivered molecule must be a polynucleotide, nucleotide, or a polysaccharide are obvious in view of compositions comprising a fatty acid or amide leaving group as well as a polynucleotide nucleotide, or polysaccharide leaving group as allowed for at column 9, line 16 to column 10, line 2. The fatty acid or amide moiety accounts for R1. See attached search result and column 23, lines 57-65. Nucleic acid attachment is exemplified at the nucleobase via an amine group, and at a 5' phosphate position, but other sites of attachment are considered to be obvious variants to one of ordinary skill in the art. Similarly modification of the nucleic acid to provide other types of reactive groups as listed in instant claim 12 is considered to be obvious in view of the teachings of Lucas from column 24, line 566 to column 25, line 9, which discloses modification of the leaving group (i.e. nucleic acid) for attachment to an indicator group (e.g. rhodamine or fluorescein). The compositions are transported into both human and tumor cells. See paragraphs 113 and 107. The compositions may be admixed to provide proper osmolality and may contain additives such as enzyme inhibitors. See column 28, lines 15-41. Claims 24-26 are included in this rejection because the compositions of Lucas meet the physical characteristics required by these claims.

Lucas does not teach conjugates comprising oligonucleotides.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use oligonucleotides in the invention of Lucas. One would have been motivated to do so in order to assay a given cell for the activity of a nuclease and an esterase. For example, Pitt teaches that various hydrolytic enzymes such as RNases and esterases are released from cytoplasmic organelles as a result of viral infection, so

it would have been obvious to use the invention of Lucas to assay simultaneously both these activities as an indicator of infection or of organelle integrity. It would have been obvious to substitute an oligonucleotide for a polynucleotide, as these compounds are art recognized equivalents, i.e. they are both degraded by nucleases. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).

Response to Arguments

Applicant's arguments filed 2/26/04 have been fully considered but they are not persuasive.

Applicant argues that Iyer fails to teach compositions that are stable in vivo. This is unpersuasive for the following reasons. The scope of the term "stable" is not defined in the specification or claims, and has therefore been interpreted to its fullest reasonable breadth. Thus stability can be measured in the context of time. In Iyer (1996), conjugates comprising the claimed attachment structures are completely stable in the presence of porcine liver esterase for at least 23 minutes, and most of the conjugate remains unhydrolyzed after incubation for 6 hours. See Fig. 3, panels A and B on page 1921. Similarly, Iyer (1997) shows that most of the conjugate comprising the claimed attachment is stable for at least 20 hours in the presence of pig liver esterase. See Fig.

5B on page 875. Thus one of ordinary skill in the art would reasonably expect that the compositions of Iyer would be stable for some period of time in vivo, and that period of time would be directly related to the esterase activity in the in vivo location.

Applicant's remarks regarding the standing rejections over Lucas are directed to the stability of the compositions of Lucas, and to the breadth of the teachings of Lucas as it affects the obviousness of the claimed compositions. These arguments were addressed above under 35 USC 102 rejections.

For these reasons the rejections are maintained.

Conclusion

No claim is allowed. Claims 8 and 9 are free of the art of record. Claim 9 would be allowable if it ended in a period.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached at 703-306-3217. The official central fax number is 703-872-9306. Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER